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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,750	12/05/2005	Yoichi Matsubara	10939/2192	5376

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PAULA EVANS/
C/O SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, SEARS TOWER
CHICAGO, IL 60606-1080

EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,750	MATSUBARA ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 12-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 30, 2007 that includes a response to the final office action dated January 10, 2007 has been entered. Claims 1-10 and 12-20 are pending in the application. Claims 1, 4, 10, 12, 15 and 16 have been amended, and claim 11 cancelled. Claims 18-20 have been newly added.

Claims 1-10 and 12-20 are under current examination.

Response to Claim Rejections - 35 USC § 112- New Matter

Claims 10-12 and 16 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement and containing new matter, in the previous office action dated January 10, 2007. Applicants' cancellation of claim 11 renders its rejection moot. In view of Applicants' amendments of claims 10 and 16, to delete the term "substantially"; and deletion of "at least one labeled primer", thus obviating the issue of new matter, the previous rejections are hereby withdrawn.

Response to Claim Rejections - 35 USC § 112- Second Paragraph

Claims 10 and 15 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite, in the previous office action dated January 10, 2007. In view of Applicants' amendments of claims 10 and 15, to delete the terms "substantially", and "about", thus obviating the grounds for rejection, the previous rejections are hereby withdrawn.

Response and New Claim Rejections - 35 USC § 103

Applicant's claim amendments have necessitated the following new grounds of rejection.

Claims 1, 3, 4, 6-12, 14 and 16 stand rejected and claim 18 is newly rejected under 35 U.S.C. §103(a) as being unpatentable over Link et al. (U.S. Patent No: 5,635,347; Jun 3, 1997), in view of Klepp et al. (Biochemica 2:14-16; 2000), and further in view of Fu et al. (U.S. Patent No: 6,583,112; filed July 17, 2000), Applicants' cancellation of claim 11 renders its rejection moot. The rejection set forth on pp. 4-7 of the previous office action dated January 10, 2007 is maintained for claims 1, 3, 4, 6-10, 12, 14 and 16 and further applied to newly added claim 18 for reasons of record.

Applicants traverse the rejection, arguing that Link does not teach or suggest all the elements of claim 1. Specifically that Link teaches that optimal primer size is about 20-30 bases in length and teaches away from the solution claimed, because Link discourages use of smaller primers due to increases in non-specific hybridization. Applicants' arguments have been fully considered, but are not found persuasive.

Applicants have again argued against the references individually. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Just as we look to a chemical and its properties when we examine the obviousness of a composition of matter claim, it is this invention as a whole, and not some part of it, which must be obvious under 35 U.S.C.103." *In re Antonie*, 559 F.2d 618, 620, 195 USPQ 6,8 (CCPA 1977). By ignoring the analysis of the rejection as whole, Applicants have incorrectly extended the teachings of Link et al. with respect to primer length, to probe length. The instant claims are directed to a method comprising the steps of amplifying a DNA sequence using primers and hybridizing the amplified DNA to a hybridization probe with a length of 10-15 bases. Thus it is the probe length that is size limited in the instant claims and not the primers. Applicants' arguments are therefore not on point.

For completeness of record, it should be noted that Link does not discourage the use smaller primers, because Link et al state: "The optimal primer size is typically about

20-30 bases in length, but workable primers may be smaller or larger in particular circumstances." (second column, lines 13-16). Thus primer size may be varied depending upon the paradigm to be addressed.

Applicants additionally state that as acknowledged by the Office, Link fails to teach or suggest a labeled 10-15mer hybridization probe. Such is not the case, the previous office action stated that Link: "do not describe the detection of the hybrid following probe hybridization, by affinity chromatography on a test strip and do not restrict the length for the probe to any particular size" (p. 5).

Applicants further argue that Link fails teach or suggest a hybridization probe with a Tm of 25°C to 40°C lower than the Tm of primers used in the DNA amplification...Just because the Tm of the hybridization probe may be 25°C to 40°C lower than the Tm of primers does not establish inherency of that requirement. As such, the Office has failed to show how Link expressly or inherently provides for the Tm requirement of claim 1. Such is not found persuasive, because the obviousness rejection is not limited to the teachings of Link et al. As indicated in the foregoing discussion, Link et al. do not restrict the length for the probe to any particular size, but do teach primer sizes of 20-30 bases in length, or larger. Fu et al. teach allele-specific oligonucleotide probes, that may be as few as 12 nucleotides in length. Thus, given the size differential between the probe size and primer sizes taught by the prior art, in consideration of the fact that the degree to which the Tm of the labeled primer would be lower than that of any given primer would depend both on the length and the sequence composition of the probe sequence, as well as the buffer or ionic concentration of the hybridization reaction, all of which are within the control of the design by a person of ordinary skill in the art, as indicated by Fu et al., the Tm of the hybridization probe would necessarily be lower than the Tm of the labeled primer. Exactly how much lower would depend on the variables already stated. It should be noted that the primers used in the working examples are 20 and 25 bases in length (Table 1) and the probes are in the 11-17 base length range (Table 2). Link et al. and Fu et al. teach primer and probe lengths consistent with those taught in the instant specification. Thus, the Tm of the probes taught in the prior art must necessarily encompass the Tm of the probes taught by the instant specification.

Applicants argue against the reference of Klepp individually, stating that Klepp does not teach or suggest all elements of claim 1, because Klepp does not teach or suggest hybridizing the amplified DNA to a hybridization probe with length of 10 - 15 mer, and Klepp teaches away from such feature by requiring that the "size of the labeled oligonucleotide [hybridization probe] must range between 17 - 40 bases". Because Klepp discourages use of a hybridization probe less than 17 bases in length ("must range between 17-40 bases"), and does not disclose any other alternative, Klepp teaches away from the requirement in claim 1 that the hybridization probe be a 10-15mer.

Applicants' arguments are not found persuasive, because Klepp is actually not rigid in his teachings for an oligonucleotide of 17-40 bases, as the statement continues: "Longer oligonucleotides require optimization with regard to probe concentration and hybridization conditions". Thus it is clear that the 17-40 base requirement is not rigid and may be considered flexible if probe concentration and hybridization conditions are optimized. Further, an analysis of the prior art as a whole requires the analysis of the teachings of all the references combined. In an obviousness rejection, Klepp is not required to teach each and every element of claim 1.

As previously noted that Klepp is a publication guideline for a commercial test strip product. As such, the publication specifies optimal conditions for achieving a signal following hybridization of the probe to the target PCR product.

Klepp actually discloses more than one alternative by allowing for oligonucleotides outside the 17-40 base range, and does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed There is no teaching or suggestion by Klepp that a probe length of less than 17 mer would not work. While both the prior art of record and the instant specification note that shorter probe lengths result in poorer signal to noise ratios, the prior art of Fu et al. teaches that hybridization probes as short as 12 mer may be utilized, based on the particular application and design by a person of ordinary skill in the art. Thus, a person of ordinary skill in the art in considering the teachings from the totality of the prior art would not be taught away by the teachings of Klepp.

In response to Applicants' argument that Klepp fails to teach or suggest a hybridization probe with a Tm of 25°C to 40°C lower than the Tm of primers used in the DNA amplification, Applicants are referred to the reply previously provided in the foregoing discussion.

Applicants argue against the reference of Fu et al. individually, stating that Fu does not teach or suggest all elements of claim 1, because Fu does not teach or suggest all the features of claim 1; that Fu does not teach or suggest labeling a primer with a first labeling agent; a labeled hybridization contained in a DNA amplification reaction solution; detection of the hybrid with both a first and a second labeling agent; detection of the hybrid affinity chromatography, or a hybridization probe with a Tm of 25°C to 40°C lower than the Tm of primers used in the DNA amplification. Applicants' arguments are not found persuasive, because had Fu et al. taught the missing limitations, the reference would have been applied under 35 U.S.C. 102.

Each of the limitations cited by Applicants as missing from Fu et al. has been taught by the other references cited in the obviousness rejection, or addressed in the foregoing reply.

Applicants further argue that the office has failed to provide a reason to combine or modify the methods of Link, Klepp, or Fu so as to reach the requirements of claim 1. Citing *KSR Intl Co.*, Applicants additionally argue that the Office has failed to provide any need or problem, nor any resultant advantage, that would provide a reason to provide for 10-15mer labeled primers and a hybridization probe with a Tm of 25°C to 40°C lower than the Tm of primers used in the DNA amplification, as required by claim 1, especially in light of references teaching away from such modification. The Office merely asserts that selection of short hybridization probes would be a "matter of design choice" but provides no rationale to support such a statement. Applicants' arguments have been fully considered, but are not found persuasive.

Applicants' arguments with regard to teaching away have been addressed above. With regard to the motivation to combine the reference, such was provided in the previous office action, stating: "The methods described by both Link et al. and Klepp et al. are directed to the PCR amplification and detection of sequences using differentially

labeled primer and hybridization probes, and the methods of Link et al. and Fu et al. are directed to detection of gene mutations, including point mutations. Thus a person of ordinary skill in the art would be motivated to combine the mutation detection method of Link et al. using the short hybridization probes taught by Fu et al., as a matter of design choice, and the test strip affinity chromatographic method of Klepp, to rapidly detect a mutation following amplification and hybridization." As set forth in the rejection, Fu et al. describe probes and primers for detecting WRN genes and mutants thereof, wherein the probes are capable of hybridizing under conditions of either high or moderate stringency. The authors state that the cellular nucleic acid is subjected to an amplification procedure, such as PCR and the mutants of WRN may be detected by hybridization with allele-specific oligonucleotide probes, that may be as few as 12 nucleotides in length, usually about 14 to 18 nucleotides in length. They additionally state that the selection of probe size is somewhat dependent upon the use of the probe, and is within the skill of the art (columns 3 and 18).

Fu et al. are not required to justify their teachings. As is evident from the teachings of Fu et al. in columns 3 and 18, the selection of probe size is dependent upon the use of the probe by one skilled in the art (i.e. a matter of design choice).

Claims 1, 2, 5, 15 and 17 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Link et al., Klepp and Fu et al. as applied to claims 1, 3, 4, 6-12, 14, 16 and 18 above, and further in view of Gunneberg et al. (Clin. Chem. 39(10):2157-2162; 1993). The rejection set forth on pp. 7-8 of the previous office action dated January 10, 2007 is maintained for reasons of record.

Applicants request clarification of the status of claim 1 with respect to the rejection, as the Office recites several features not present in claim 1 in support of the above rejection. In response, Applicants should note that base claim 1 has been included in the rejection because the limitations present in the dependent claims must necessarily be encompassed by their base claim, as the base claim is broader than the claims dependent there from.

Applicants traverse the rejection, arguing Gunneberg does not teach or suggest all requirements of claim 1. For example, Gunneberg does not teach or suggest hybridizing the

amplified DNA to a hybridization probe with length of 10 - 15 mer having a base sequence complementary to the target base sequence to be detected, as required by claim 1. As another example, Gunneberg does not teach or suggest including a labeled hybridization probe in the DNA amplification reaction solution, as required by claim 1.

Applicants' arguments have been fully considered, but are not found persuasive, because a single reference is not required to teach all the requirements of a claim in an obviousness rejection that is based on a combination of references.

Applicants additionally argue, not only does Gunneberg require separate amplification and hybridization reactions, Gunneberg further requires sequential hybridization of the unlabeled and labeled probes; and teaches away from joint hybridization with a labeled probe and an unlabeled competitive probe by citing problems with previous studies that attempted simultaneous hybridization

As indicated in the previous office action, Gunneberg et al. in referring to previous studies using competitive assays using labeled and unlabeled oligonucleotides used simultaneously in the hybridization reaction, note the requirement for a 20-fold molar excess of unlabeled allele-specific oligonucleotide. However, this observation would not be considered a teaching away, because it is apparent that simultaneous hybridization remains effective in detecting mutations and reducing signal to noise ratio. Furthermore, a person of ordinary skill in the art would recognize from the teachings of Gunneberg et al. that simultaneous hybridization is an alternative to sequential hybridization and that an additional hybridization step could be avoided by simply increasing the amount of unlabeled allele-specific oligonucleotide in the reaction. Thus, simultaneous hybridization constitutes an effective alternative in mutation detection.

Applicants state that sequential hybridization requires a host of other experimental design parameters, which are not necessarily compatible with the disclosed method of Gunneberg; and that the Office should support the assertion that simultaneous hybridization is interchangeable with sequential hybridization in the methods of Gunneberg by citation to a reference that provides such.

In response, it should be noted that there is no requirement to incorporate simultaneous hybridization into the method of Gunneberg. The test for obviousness is not whether the features

of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). The reference of Gunneberg teaches that the presence of unlabeled oligonucleotide in a PCR reaction increased the specificity of single-point mutation detection and improved signal to noise ratio. It is this teaching that when combined with the teachings of Link, Klepp and Fu would render obvious the instant invention by Applicants.

Thus, the rejection of claims 1-10, 12 and 14-17 is maintained for reasons of record, and the foregoing discussion

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Applicant's claim amendments have necessitated the following new grounds of rejection.

Claims 1, 13, 19 and 20 are newly rejected under 35 USC 103(a) as being unpatentable over Link et al. (U.S. Patent No: 5,635,347; Jun 3, 1997), in view of Klepp (Biochemica 2:14-16; 2000) and Fu et al. (U.S.Patent No: 6,583,112; filed July 17, 2000), as applied to claims 1, 3, 4, 6-10, 12, 14 and 16 in the office action dated January 10, 2007, and further in view of Stuyver et al. (U.S. Patent Application Publication No.: 2003/0077575; filed Aug. 31, 2001).

Link et al. describe a method of detecting a nucleic acid sequence of interest in the amplification product of a PCR reaction, wherein one primer is labeled with a first label and the

PCR reaction is conducted in the presence of an alternately labeled hybridization probe. Klepp describes a DNA detection test strip for the rapid detection of labeled PCR products in a reaction mixture containing 5' digoxigenin -end labeled PCR primers and biotin labeled hybridization probe. Fu et al. describe allele-specific oligonucleotide hybridization probes that may be as few as 12 nucleotides in length for detecting WRN gene mutations, wherein the probes are capable of hybridizing under conditions of either high or moderate stringency.

Although Link et al., Klepp and Fu et al. do not teach probe lengths of 10 and 11 bases, the use of labeled oligonucleotides in the 10-15 mer range to detect PCR amplification products was well known in the prior art at the time of the instant invention. For example, Stuyver et al., in describing a method for detection of mutations in the reverse transcriptase gene, using probes for differential hybridization (Abstract), state that to detect single base pair mismatches, variations are possible in the length of the probes (paragraph [0080], p. 5), and particularly preferred lengths of probes include 10, 11, 12, 13, 14 and 15 nucleotides (paragraph [0081], p. 5). The polymorphisms detected include insertion mutation (see Fig. 1C, region III, position 69). Specifically described is the application of the probes to biotinylated PCR fragments with subsequent botin-streptavidin calorimetric detection (paragraph [0185], p. 11).

The methods described by Link et al., Klepp et al. and Stuyver et al. are directed to the PCR amplification and detection of sequences using differentially labeled primer and hybridization probes, and the methods of Link et al., Fu et al. and Stuyver et al. are directed to detection of gene mutations, including point mutations. Thus a person of ordinary skill in the art would be motivated to combine the mutation detection method of Link et al. using the short hybridization probes taught by Fu et al., and Stuyver et al. as a matter of design choice, and the test strip affinity chromatographic method of Klepp, to rapidly detect a mutation following amplification and hybridization.

Therefore, it would have been *prima facie* obvious to someone of ordinary skill in the art at the time of the instant invention to utilize the combination of the point mutation detection method of Link et al. Fu et al., and Stuyver et al., and the test strip affinity chromatographic method of Klepp, resulting in the practice of the instantly claimed invention. A person of ordinary skill in the art, would have been motivated to combine the elements of differentially labeled PCR primer and hybridization probe, together with

the detection method utilizing affinity chromatography test strip, and would have a reasonable expectation of success in detecting a mutation site in a sequence, because the PCR mediated amplification of a target sequence and specific detection of a mutation site are enabled by the procedures described by Link et al., Fu et al. Stuyver et al. and Klepp. Moreover, each limitation contained in the method of claims 1, 19 and 20 is effectively described by their combined teachings.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00-4:00 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on **(571) 272-0739**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Fereydoun G. Sajjadi, Ph.D.
Examiner, A.U. 1633

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633